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75014, Paris(54) **A Stable Composition Containing a Water-Sensitive Cosmetic and/or Skin Care Agent**

The present invention pertains to a composition intended for topical application which contains at least one water-sensitive agent with topical action and at least one polyol, with an effective amount of said polyol being present in order to obtain a level of activity in water for said composition which is less than or equal to 0.85, for the purpose of stabilizing the aforementioned water-sensitive agent, with the respective composition including at least one structure-forming agent selected among polymers and oils.

The water-sensitive agent may specifically consist of an enzyme. The composition which is to be obtained may be used for cleansing and/or treating and/or protecting skin and/or keratin fibers.

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Description

The present invention relates to a composition for topical application containing a stabilized agent which can be used within the fields of cosmetics and/or skin care for cleansing and/or treating and/or protecting skin and/or keratin fibers.

Prior art includes introduction of agents into cosmetic and/or skin care compositions for the purpose of providing specific treatments for skin and/or hair, in order to cleanse the skin, for example, or in order to counteract drying, aging, or discoloration of the skin, for treating acne or certain skin diseases (eczema, psoriasis), for counteracting stress caused by weight, for promoting restructuring of the skin or regeneration of cells, or for treating seborrhea affecting hair.

For example, prior art includes introduction of enzymes into cosmetic compositions, and especially proteases which are used for their proteolytic properties. These enzymes are often in demand within the cosmetics sector on account of their smoothing and cleansing capabilities, as well as their ability to remove dead skin cells.

Unfortunately, certain agents and especially the previously cited agents possess the disadvantage of being unstable in aqueous media and of being easily degraded or altered under the influence of water. Hence, their activity is quickly lost over the course of time, and this instability diminishes desired efficacy.

Various measures for overcoming this disadvantage have also been considered. In particular, consideration has been given to including agents, notably enzymes, within powdered compositions (Consult Document JP-A-63-130514). Moreover, most skin-cleansing products contain enzymes which exist in this form. Consideration has also been given to use of the aforementioned agents, and especially enzymes, in an immobilized form within polymer media (Consult Document JP-A-61-207499), or within microcapsules (Consult Document JP-A-61-254244). Unfortunately, some of these measures require specific series of procedures, whereby the cost of compositions and their preparation time increases.

Another approach consists of including agents within liquid anhydrous media (Consult Document US-A-5322683). Unfortunately, this approach limits the galenic form of compositions, and it does not allow incorporation of hydrophilic agents.

Hence, the need for compositions where sensitive cosmetic and/or dermatological agents would retain all of their properties and their efficacy over the course of time continues to exist.

The Applicant has discovered in a previously unanticipated manner that use of a polyol for binding an effective amount of water within a topical composition containing a water-sensitive agent so as to obtain a level of activity in water for the composition which is less than or equal to 0.85, along with at least one structure-forming agent, allows degradation of the respective agent to be prevented.

One object of the present invention also consists of a stable composition for topical application containing at least one water-sensitive agent with topical action and at least one polyol, characterized by the fact that this composition does not contain calcium salts, by the fact that a sufficient amount of said polyol is present for obtaining a level of activity in water for the composition which is less than or equal to 0.85, and by the fact that at least one structure-forming agent selected among polymers and oils shall be included.

The invention also pertains to a stable composition for topical application which contains at least one water-sensitive agent with topical action and at least one polyol, characterized by the fact that an amount of said polyol which varies from 30% to 99.99% by weight in relation to the total weight of the composition shall be present, and by the fact that it shall include at least one structure-forming agent selected among acrylic polymers, methacrylic polymers, and oils.

Indeed, it is known that water content may exercise an influence upon the stability of water-sensitive agents, but there have never been descriptions or suggestions indicating that the presence of a polyol and a structure-forming agent may prevent degradation of agents of this kind. Hence, a document by D. Tzanos ("Behavior of Enzymes by Controlling the Medium Water Activity," *Riv. Ital. Essenze, Profumi, Piante Off., Aromi, Saponi, Cosmet., Aerosol*, 1977, Volume 59, Number 5, pages 208-211) encourages technically experienced persons within the respective field to use surface-active agents for stabilizing enzymes within aqueous media or to rely upon enzyme fixation upon porous bases. In contrast, technically experienced persons are advised against using glycols.

Furthermore, Document US-A-5356800 describes an enzyme stabilization method consisting of use of a mixture containing an alcohol or a glycol, an oxyethylenated alkyldiamine, and an amino oxide. According to this document, enzyme stabilization can only be obtained by using the mixture which is described.

Moreover, Document JP-A-01-283213 describes a cleansing composition containing an enzyme and a polyol. According to this document, enzyme activity is stabilized by adding a protein, such as collagen, elastin, or albumin.

Document FR-A-1397399 describes a method of stabilizing proteases which consists of use of a mixture of polyol and a calcium salt. According to this document, the presence of a calcium salt is indispensable for protease stabilization.

Furthermore, from prior art represented by the document J. Soc. Cosm. Chem. Jap., 1993, 27(3), pp 276-288, it is known that proteases can be stabilized by chemically modifying them and, that adding polyols contributes to improvement of the stability of a modified protease.

It has not been determined, however, that, in the instance of topical compositions, degradation of water-sensitive agents can be prevented by use of sufficient amounts of polyols in combination with a structure-forming agent.

Hence, another object of the present invention is use of a sufficient amount of at least one polyol for obtaining a level of activity within water for the respective composition which is less than or equal to 0.85 within a composition intended for topical application which is devoid of calcium salts and contains at least one water-sensitive agent with topical action, along with at least one structure-forming agent selected among polymers and oils for the purpose of stabilizing the water-sensitive agent.

It is preferable for the polymer to be selected among acrylic and methacrylic polymers.

Preferably, the amount of the polyol or polyols should be sufficient for the respective composition's level of activity in water to be less than or equal to 0.7.

For a medium containing water, activity in water, or a_w , is the ratio between water vapor pressure for the product, "Product P_{H_2O} ," and the water vapor pressure of pure water, "Pure P_{H_2O} " at the same temperature. Activity in water can also be expressed as a ratio between the number of water molecules, " N_{H_2O} ," and the total number of molecules, " $N_{H_2O} + N_{\text{dissolved substances}}$," which takes molecules from dissolved substances, " $N_{\text{dissolved substances}}$," into account.

It is expressed by the following formulas:

$$A_w = \frac{\text{Product } P_{H_2O}}{\text{Pure } P_{H_2O}} = \frac{N_{H_2O}}{N_{H_2O} + N_{\text{dissolved substances}}}$$

It is possible to rely upon different methods for measuring activity in water. The most widely used method is the manometer method, with direct measurement of vapor pressure.

In a manner representing prior art, water activity within a cosmetic or dermatological composition is placed at approximately 0.95 to 0.99. Water activity below 0.85 represents a noteworthy decrease in water activity.

The polyol which is to be used according to the invention may be specifically selected among glycerin and glycols, and particularly propylene glycol and polyethylene glycols.

The amount of polyol(s) to be used in a composition according to the invention depends upon the type of composition (gel or emulsion) and upon its other ingredients. This amount should be sufficient for attaining the desired water activity level. The polyol or polyols which are to be used according to the invention are preferably present in an amount representing at least 30% by weight, and preferably varying from 40% to 99.99% by weight, or, even more preferably, from 60% to 80% by weight in relation to the total weight of the respective composition.

According to a preferred embodiment of the invention, one or more polyols are wholly or partially present in a complexed form with an acrylic or methacrylic polymer. This polymer may also include bonded water; in other words, it may be combined with a mixture of water and polyol(s).

The term acrylic or methacrylic polymer refers to an acrylic or methacrylic acid homopolymer or copolymer, or a copolymer of an acrylic or methacrylic acid derivative.

The amount of polymers along with the polyol or polyols and bonded water in applicable instances shall preferably extend from 70% to 99.99% by weight within a composition according to the invention, and even more preferably from 80% to 95% by weight in relation to the total weight of said composition.

As homopolymers where water-polyol complexing has occurred, it is possible to cite homopolymers sold under the designations *Norgel* and *Lubrajel CG* by the company known as *Guardian*. These polymers are complexed glyceryl polyacrylates with more than 65% glycerin and/or propylene glycol, and less than 35% water by weight. The aforementioned polymers provide a polyol and water in a complexed form, and they also perform the role of a gelling agent for a composition when necessary.

Comparative tests that are presented subsequently demonstrate that only compositions whose water activity level is at least equal to 0.85 can allow proper preservation of the activity of water-sensitive topical agents, and especially proper preservation of enzyme activity among enzymes.

Water-sensitive agents which can be used according to the present invention specifically include enzymes (for example lactoperoxidase, lipase, protease, phospholipase, and cellulases), natural extracts such as green tea, lemon balm extract, thyme extract, procyanidole oligomers (PCO's), such as hawthorn PCO, pine PCO, and grape PCO, vitamins, including ascorbic acid (Vitamin C) and its esters in particular, retinol (Vitamin A) and its esters, phosphate and glucosylated derivatives, urea, and rutin.

It is advantageous for the water-sensitive agent or agents which are being used to be enzymes, and, most specifically, forms of protease. For example, proteases can be selected from the protease sold under the commercial designation "*Subtilisine SP 544*" by the *Novo Nordisk* company and the form sold under the commercial designation "*Lysoveg*" by the company known as *Laboratoires Serologiques de Nancy*.

The amount of a water-sensitive agent which is to be included in a composition according to the invention depends upon the type of agent being used. In general terms, it is possible for one or more agents to be used in a composition according to the invention in amounts varying from 0.001% to 15% by weight, preferably from 0.01% to 10%, and, more preferably, from 0.05% to 5% by weight in relation to the total weight of the respective composition.

As oils which can be used according to the invention, it is possible to cite mineral oils (vaseline oil), vegetable oils (jojoba oil), animal oils, synthetic oils (decyl oleate), silicone oils (cyclomethicone, polydimethylsiloxane, dimethicone), and fluorinated oils (perfluoropolyethers). The respective oil or oils can be present in amounts varying from 5% to 60% and preferably from 5% to 40% by weight in relation to the total weight of the composition.

In addition, a composition according to the invention may contain one or more salts whose presence shall allow further improvement of the stability of the agent which this composition contains. As salts, it is possible to cite magnesium salts and sodium salts in particular, and, more specifically, magnesium sulfate, magnesium chloride, and sodium chloride. An amount of salt or salts varying from 0.1% to 30% may be present, and preferably an amount varying from 2% to 12% by weight in relation to the total weight of the composition.

A composition according to the invention contains a topically acceptable medium, namely one which is compatible with skin and hair, while specifically being an ingredient in compositions used for cleansing, protection, treatment, or care for the skin and/or hair, and particularly for the face, neck, hands, hair, and scalp, or for the body, as well as for eyelashes.

Another object of the present invention also includes use of a composition according to the invention for cleansing and/or protecting skin and/or keratin fibers, in other words, for hair and/or eyelashes.

Another object of the present invention also consists of a cleansing composition for skin and/or keratin fibers which contains at least one water-sensitive cleansing agent and at least one polyol, characterized by the fact that it does not contain calcium salts, with said polyol being present in an effective amount for obtaining a water activity level for the composition which is less than or equal to 0.85, while also containing at least one structure-forming agent selected among polymers and oils.

Lastly, another object of the invention consists of a cosmetic and/or dermatological method of cleansing and/or protecting skin and/or keratin fibers, characterized by the fact that said method consists of applying a composition which is free from calcium salts to skin and/or keratin fibers, with the respective composition containing at least one water-sensitive agent with topical action, at least one polyol which is present in an effective amount for obtaining a water activity level for said composition which is less than or equal to 0.85, for the purpose of stabilizing the aforementioned water-sensitive agent, and at least one structure-forming agent selected among polymers and oils.

A composition according to the invention may also exist specifically in the form of a solution, a gel, or a water-in-oil or oil-in-water emulsion constituting creams, balms, lotions, or milks. This composition may also include microcapsules, microparticles, or lipid vesicles of the ionic and/or nonionic type. These various types of compositions are prepared according to the usual methods.

The aforementioned compositions specifically constitute creams for protection, treatment, or care of the face, the hands, and the feet, body milks for protection or care, or lotions, gels, or foams for treating skin, mucous membranes, hair, and the scalp.

When a composition to which the invention pertains consists of an emulsion, the portion of the oleaginous phase may vary from 10% to 80% by weight, and preferably from 20% to 40% by weight in relation to the total weight of said composition. This emulsion shall preferably include at least one dispersant selected among emulsifiers, vesicles, and particles. Oils, emulsifiers, and ultimately coemulsifiers which may be used in a composition possessing the form of an emulsion are to be selected among those which are traditionally used in the fields of cosmetics and skin care. Emulsifiers and coemulsifiers may be present within a composition in a proportion varying from 1% to 10% by weight, and preferably from 2% to 6% by weight in relation to the total weight of the respective composition.

In a manner representing prior art, it is also possible for a composition according to the invention to contain customary additives within the fields of cosmetics and skin care, such as surface-active agents, especially foaming surface-active agents, hydrophilic or lipophilic agents in addition to water-sensitive agents, preservation agents, anti-oxidants, solvents, fragrances, fillers, filters, odor absorption agents, and coloring materials. Amounts of these additives are those which are traditionally adopted within the respective fields, for example as from 0.01% to 15% of the total weight of a given composition. Depending upon their nature, additives may be introduced during the oleaginous phase, the aqueous phase, and/or within lipid vesicles.

In addition to the previously indicated oils, it is possible for the oleaginous phase to include oily substances such as fatty alcohols (stearic acid) and waxes (silicone wax).

Among foaming surface-active agents which may be used in the present invention, disodium cocoamphodiacetate (*Miramol C2M*, which is sold by the company known as *Rhone-Poulenc*) and 55% glucose decyl ether in water (*Oramix NS10*, which is sold by the company known as *Seppic*) can be cited as examples. The water content of these raw materials is included within the total amount of water in a given composition.

As emulsifiers which may be used in the present invention, it is possible to cite siliconized emulsifiers, such as alkyldimethicone copolyols, for example, which include cetyldimethicone copolyol, which is sold by the company known as *Goldschmidt* with the designation *Abil EM-90*, or a dimethicone copolyol-cyclomethicone mixture, which is sold by *Dow Corning* with the designation *3225C Formulation Aid*.

Examples of hydrophilic agents which may be used include proteins or protein hydrolysates, amino acids, allantoin, sugars and sugar derivatives, and starch.

Examples of lipophilic agents which may be used include tocopherol (Vitamin E) and its derivatives, essential fatty acids, ceramides and essential oils.

Stability Test for Enzyme Activity

The activity of an enzyme included within an aqueous gel according to the invention and in two comparison gels was measured by using the casein method. According to this method, casein which is used as a substrate undergoes hydrolysis by an enzyme, with releasing of amino acids which are subsequently quantified by means of colorimetry with use of Folin-Ciocalteu reagent. Colorimetric absorbance readings increase according to how high the enzyme amount may be.

The gels which were tested contained 1% protease (*SP 544* protease) by weight, and they possessed the following composition:

- Gel I (according to the invention): 99% *Norgel* (or 0.99% acrylic polymer, 66.3% polyol, and 30.7% water) and 1% protease.
- Gel II (comparison product): 99% esterified propylene glycol in an 80% to 85% proportion, in a 0.5% solution in water, and 1% protease.
- Gel III (comparison product): 99% polysaccharide (*Fucogel 1000*: biosaccharide gum-1, sold by the company known as *Solabia*; it is based upon fucose, galactose, and galacturonic acid), and 1% protease.

The following table provides percentage results for remaining enzyme activity after two months:

Gel	Activity of gel in water— a_w	% of enzyme activity
Gel I	0.65	71%
Gel II	0.989	0%
Gel III	0.967	0%

These results demonstrate that only Gel I, which embodies the invention, allows preservation of protease enzyme activity.

The following examples of compositions according to the invention are provided for illustrative purposes without being of a restrictive nature. Quantities are indicated according to percentages by weight.

Example 1: Gel

Norgel	85%
Subtilisine SP 544	0.1%
Water	q.s.p. 100%

A translucent gel which can be used as an exfoliant gel is obtained. Its activity level within water is 0.735 +/- 0.05.

Subtilisine SP 544's enzyme activity level is still 80% after two months at ambient temperature.

Example 2: Water-in-oil emulsion

Aqueous phase:

Norgel	71.5%
NaCl	0.5%

Oleaginous phase:

Cetyldimethicone copolyol (<i>Abil EM-90</i> , sold by the <i>Goldschmidt</i> company (emulsifier)	2%
Jojoba oil	4%

Polydimethylsiloxane	8%
Vaseline oil	10%
Decyl oleate	3.9%
<i>Subtilisine SP 544</i>	0.1%

The following method is employed for preparing the emulsion: the aqueous phase is prepared at one point, and the oleaginous phase is prepared at another point, with the aqueous phase being emulsified within the oleaginous phase at ambient temperature by stirring with a homogenizer.

A white cream which is suitable for promoting removal of skin cells and highlighting the complexion is obtained. Its water activity level is 0.62 +/- 0.02.

After two months at ambient temperature, the enzyme activity level of *Subtilisine SP 544* is still 100%.

Example 3: Cleansing gel

Subtilisine SP 544	0.04%
Norgel	83%
Miranol C2M (sold by the company known as <i>Rhone-Poulenc</i>)	16%
Water	q.s.p. 100%

A foaming cleansing gel for the face and the body, which is rinsable with water, is obtained. Its water activity level is 0.67 +/- 0.02.

Example 4: Cleansing gel

Norgel	88.97%
Lysoveg	0.03%
Oramix NS10 (sold by the company known as <i>Seppic</i>)	11%

A foaming cleansing gel for the face and the body, which is rinsable with water, is obtained. Its water activity level is 0.68 +/- 0.02.

Example 5: Water-in-oil emulsion*Oleaginous phase:*

Dimethicone copolyol and cyclomethicone (" <i>3225C Formulation Aid</i> ," which is sold by <i>Dow Corning</i>)	22.6%
Dimethicone	4.9%
Mineral oil	3%

Aqueous phase:

Glycerin	45.5%
Magnesium sulfate (stabilizer)	2%
<i>Subtilisine SP 544</i>	0.05%
Propylene glycol	8%
Water	q.s.p.100%

The emulsion is prepared in the same manner as Example 2.

A white cream is obtained for smoothing the skin, and its water activity level is 0.63 +/- 0.02.

After two months at ambient temperature, the enzyme activity level of *Subtilisine SP 544* is still 90%.

Example 6: Water-in-oil emulsion*Oleaginous phase:*

Dimethicone copolyol and cyclomethicone (" <i>3225C Formulation Aid</i> ," which is sold by <i>Dow Corning</i>)	22.8%
Dimethicone and trimethylsiloxysilicate (" <i>593 Fluid</i> ," sold by <i>Dow Corning</i>)	5%
Octyl palmitate	6.7%
Corn starch	8%
Nylon-12	5%

Aqueous phase:

Glycerin	8%
Propylene glycol	8%
Magnesium chloride	6%
<i>Subtilisine SP 544</i>	0.1%
Water	q.s.p.100%

The emulsion is prepared in the same manner as in Example 2.

A white cream for smoothing the skin is obtained, and its water activity level is 0.75 +/- 0.02.

In the preceding examples, it would be possible, according to the invention, for *Subtilisine 544* to be replaced by other enzymes, ascorbic acid, green tea, and other water-sensitive agents which have been cited previously.

Claims

1. A stable composition for topical application which contains at least one water-sensitive agent with topical action and at least one polyol, characterized by the fact that it does not contain calcium salts, by the fact that an effective amount of the aforementioned polyol is present for obtaining a water activity level for the respective composition which is less than or equal to 0.85, and by the fact that at least one structure-forming agent selected among polymers and oils shall be included.
2. A composition according to Claim 1, characterized by the fact that an effective amount of the polyol for obtaining a water activity level for the respective composition which is less than or equal to 0.7 shall be present.
3. A composition according to Claim 1 or 2, characterized by the fact that the amount of the polyol which is present shall be at least 30% by weight in relation to the total weight of said composition.
4. A composition according to any of the preceding claims, characterized by the fact that the polymer is to be selected among acrylic and methacrylic polymers.
5. A stable composition for topical application which contains at least one water-sensitive agent with topical action and at least one polyol, characterized by the fact that said polyol shall be present in an amount varying from 30% to 99.99% by weight in relation to the total weight of

said composition, and by the fact that the composition shall include at least one structure-forming agent selected among acrylic polymers, methacrylic polymers, and oils.

6. A composition according to any of the preceding claims, characterized by the fact that the aforementioned polyol is selected from a group consisting of glycerin and glycols.
7. A composition according to any of the preceding claims, characterized by the fact that the polymer shall also include bonded water.
8. A composition according to any of the preceding claims, characterized by the fact that the polymer, the polyol, and bonded water shall be present in an amount varying from 70% to 99.99% by weight in relation to the total weight of said composition.
9. A composition according to any of the preceding claims, characterized by the fact that an amount of oil varying from 5% to 60% by weight in relation to the total weight of said composition shall be present.
10. A composition according to any of the preceding claims, characterized by the fact that the respective oil is to be selected among mineral oils, plant oils, animal oils, synthetic oils, silicone oils, and fluorinated oils.
11. A composition according to any of the preceding claims, characterized by the fact that the water-sensitive agent with topical action is to be selected from a group which includes enzymes, natural extracts, procyanidole oligomers, vitamins, phosphatic and glucosylated derivatives, urea, and rutin.
12. A composition according to the preceding claim, characterized by the fact that the water-sensitive agent with topical effects shall be selected from a group which includes a protease, green tea, ascorbic acid, retinol, and its esters.
13. A composition according to any of the preceding claims, characterized by the fact that the water-sensitive agent shall be present in a concentration varying from 0.001% to 15%% by weight in relation to the total weight of said composition.
14. A composition according to any of the preceding claims, characterized by the fact that it shall also include at least one salt selected among magnesium salts and sodium salts.
15. A composition according to any of the preceding claims, characterized by the fact that it shall also include at least one lipophilic or hydrophilic additive selected among preservation agents, anti-oxidants, fragrances, fillers, filters, sequestrants, essential oils, coloring materials, hydrophilic or lipophilic agents, and lipid vesicles.
16. A composition according to any of the preceding claims, characterized by the fact that it is provided in the form of an emulsion and that it likewise includes at least one dispersant selected among emulsifiers, vesicles, and particles.
17. A cleansing composition for skin and/or keratin fibers which contains at least one water-sensitive cleansing agent and at least one polyol, characterized by the fact that it does not contain calcium salts, by the fact that the respective polyol is present in an effective amount for obtaining a water activity level for said composition which is less than or equal to 0.85, and by the fact that it includes at least one structure-forming agent selected among polymers and oils.

18. Use of a composition according to any of the claims identified as 1 to 16, for cleansing and/or protecting skin and/or keratin fibers.
19. Use of at least one polyol in an effective amount for obtaining a water activity level for the respective composition which is less than or equal to 0.85 and at least one structure-forming agent selected among polymers and oils, for the purpose of stabilizing the water-sensitive agent, within a composition intended for topical application which does not contain calcium salts while containing at least one water-sensitive agent with topical action.
20. Use according to Claim Number 19, characterized by the fact that the respective polymer shall be selected among acrylic and methacrylic polymers.
21. A cosmetic method of cleansing and/or protecting skin and/or keratin fibers, characterized by the fact that it consists of applying to skin and/or keratin fibers a composition which does not contain calcium salts, while containing at least one water-sensitive agent with topical action, at least one polyol which is present in an effective amount for obtaining a water-activity level for said composition which is less than or equal to 0.85, for the purpose of stabilizing the water-sensitive agent, and at least one structure-forming agent selected among polymers and oils.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number:
EP 96 40 1431

DOCUMENTS CONSIDERED TO BE PERTINENT

Category	Reference to document, with indication of pertinent sections, if necessary	Relevant Claim	CLASSIFICATION OF APPLICATION (Int. Classification)
D, Y	CHEMICAL ABSTRACTS, Vol. 120, No. 26, June 27, 1994 Columbus, Ohio, U.S. Abstract Number 330796h Takuji Masunaga <i>et al.</i> , "The Protease as a Cleansing Agent and Its Stabilization by Chemical Modification," Page 484, XP002016491 Abstract* & J. SCCJ Vol. 27, No. 3, 1993, Tokyo, pages 276-288	1, 6, 8-21	A61K7/48
D, Y	FR-A-1 397 399 (MOMOTAMI JUNTENKAN CO., LTD.) *Entire document.	1, 6, 8-21	
A	CHEMICAL ABSTRACTS, April 2, 1990 Columbus, Ohio, U.S.; Abstract No. 12493k Page 398; XP002016492 & Jp-A-01 238 510 (TAKARA SHUZO CO., LTD.) September 22, 1989	1,6, 8-21	Areas of Technology Being Investigated (Int. Cl. 6): A61K
A	PATENT ABSTRACTS OF JAPAN Vol. 13, No. 515 (C-655), [3863], 17 November, 1989 & JP-A_01 207220 (LION CORP.), August 21, 1989 *Abstract*	1-21	

The present report has been prepared for the entirety of the claims.

Search Site:

The Hague

Date for Completion of Search:

October 22, 1996

Examiner:

J. Henry

DOCUMENT CATEGORIES CITED:

X: Especially pertinent on its own terms
Y: Especially pertinent in conjunction with another document from the same category
A: Technological background
O: Non-written disclosure
P: Inserted document

T: Theory or principle underlying the invention
E: Prior patent document published on the filing date or after said date
D: Cited within application
L: Cited for other reasons
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&: Member of the same group, related document